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(54) **INDOLE DERIVATIVES AND THEIR USE AS MCP-1 RECEPTOR ANTAGONISTS**

INDOLDERIVATE UND IHRE VERWENDUNG ALS MCP-1 REZEPTOR ANTAGONISTEN

DERIVES D'INDOLE ET LEUR UTILISATION COMME ANTAGONISTES VIS-A-VIS DU RECEPTEUR MCP-1

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Description

[0001] The present invention relates to chemical compounds, to their production as well as to pharmaceutical compositions containing them as well as to their use in therapy, in particular of inflammatory disease.

[0002] MCP-1 is a member of the chemokine family of pro-inflammatory cytokines which mediate leukocyte chemotaxis and activation. MCP-1 is a C-C chemokine which is one of the most potent and selective T-cell and monocyte chemoattractant and activating agents known. MCP-1 has been implicated in the pathophysiology of a large number of inflammatory diseases including rheumatoid arthritis, glomerular nephritides, lung fibrosis, restenosis (International Patent Application WO 94/09128), alveolitis (Jones et al., 1992, *J. Immunol.*, **149,** 2147) and asthma. Other disease areas where MCP-1 is thought to play a part in their pathology are atherosclerosis (e.g. Koch et al., 1992, *J. Clin. Invest.*, **90,** 772-779), psoriasis (Deleuran et al., 1996, *J. Dermatological Science,* **13,**. 228-236), delayed-type hypersensitivity reactions of the skin, inflammatory bowel disease (Grimm et al., 1996, *J. Leukocyte Biol.*, **59,**. 804-812), multiple sclerosis and brain trauma (Berman et al, 1996, *J. Immunol.*, **156,**. 3017-3023). An MCP-1 inhibitor may also be useful to treat stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection.

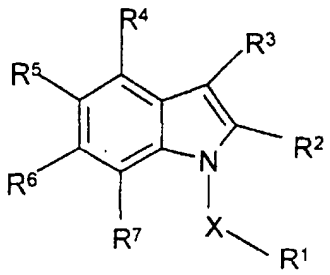
[0003] MCP-1 acts through the MCP-1 receptor (also known as the CCR2 receptor). MCP-2 and MCP-3 may also act, at least in part, through the MCP-1 receptor. Therefore in this specification, when reference is made to "inhibition or antagonism of MCP-1" or "MCP-1 mediated effects" this includes inhibition or antagonism of MCP-2 and/or MCP-3 mediated effects when MCP-2 and/or MCP-3 are acting through the MCP-1 receptor.

[0004] Copending International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341 describe and claim groups of compounds based upon the indole ring structure which are inhibitors of MCP-1 and therefore have applications in therapy.

[0005] The use of certain indole derivatives as NMDA antagonists is described is USP5051442, WO9312780, EP-483881. Other indoles and their use as inhibitors of leukotriene biosynthesis is described in for example, EP-A- 275-667.

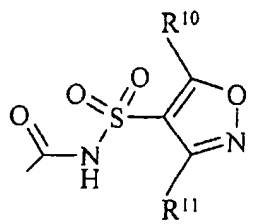
[0006] The applicants have found a particular substitution on the indole ring produces advantageous results when used therapeutically as inhibitors of MCP-1.

[0007] According to the present invention there is provided a compound of formula (I)



(I)

X is CH_2 or SO_2 R^1 is an optionally substituted aryl or heteroaryl ring; R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tetrazol-5-yl, SO_3H, or a group of formula (VI)



(VI)

where R^8 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{12}$ where R^{12} is alkyl, aryl, heteroaryl, or haloalkyl, or R^8 is a group $-(CHR^{13})_r-COOH$ where r is an integer of 1-3 and each R^{13} group is independently selected from hydrogen or alkyl; R^9 is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl, aryl, heteroaryl or haloalkyl; R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl;

R^3 is hydrogen, a functional group, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkoxy, optionally substituted aralkyl, optionally substituted aralkyloxy, optionally substituted cycloalkyl;

R^4 is a group $C(O)NR^{15}R^{16}$ or a group $(CH_2)_t R^{17}$;

where R^{15} and R^{16} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl or optionally substituted heterocyclyl provided that R^{15} and R^{16} are not both hydrogen, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms;

R^{17} is selected from $NR^{18}R^{19}$, OR^{20} or $S(O)_SR^{21}$

where R^{18} and R^{19} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{18} and R^{19} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms;

R^{20} is substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl or optionally substituted heterocyclyl,

R^{21} is optionally substituted hydrocarbyl or optionally substituted heterocyclyl,

s is 0, 1 or 2 and t is an integer of from 1-4;

[0008] R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclyl groups.

[0009] In addition, the invention provides a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, or amide of the compound of formula (I).

[0010] Compounds of formula (I) are inhibitors of monocyte chemoattractant protein-1. In addition, they appear to inhibit RANTES induced chemotaxis. RANTES is another chemokine from the same family as MCP-1, with a similar biological profile, but acting though the CCR1 receptor. As a result, these compounds can be used to treat disease mediated by these agents, in particular inflammatory disease. Thus the invention further provides a compound of formula (I) for use in the treatment of inflammatory disease.

[0011] In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. These groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

[0012] The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocylic groups such as phenyl and naphthyl. The term "heterocyclyl" or "heterocyclic" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Nitrogen heteroatoms may be substituted for example with hydrogen or hydrocarbyl depending on the available bonds. Sulphur atoms may be in the form of S, S(O) or $S(O)_2$.

[0013] Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

[0014] "Heteroaryl" refers to those groups described above which have an aromatic character. The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

[0015] Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

[0016] The term "functional group" refers to reactive substituents. They may comprise electron-donating or electron-withdrawing. Examples of such groups include halo, cyano, nitro, $C(O)_nR^{22}$, OR^{22}, $S(O)_mR^{22}$, $NR^{23}R^{24}$, $C(O)NR^{23}R^{24}$, $OC(O)NR^{23}R^{24}$, $-NR^{23}C(O)_nR^{22}$,$-NR^{22}CONR^{23}R^{24}$, $-N=CR^{22}R^{23}$, $S(O)_mNR^{23}R^{24}$ or $-NR^{23}S(O)_mR^{22}$ where R^{22}, R^{23} and R^{24} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{23} and R^{24} together form an optionally substituted heterocyclic ring as defined above, which optionally contains further heteroatoms such as sulphur, S(O), SO_2, oxygen and nitrogen, n is an integer of 1 or 2, m is an integer of 1-2.

[0017] Suitable optional substituents for hydrocarbyl or groups R^{22}, R^{23} and R^{24} include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or $S(O)_mR^{25}$ where m' is 1 or 2 and R^{25} is alkyl.

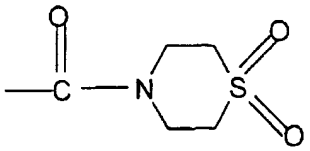
[0018] Where R^{23} and R^{24} form a heterocyclic group, this may be optionally substituted by hydrocarbyl such as alkyl as well as those substituents listed above for hydrocarbyl groups.

[0019] Suitable substituents for hydrocarbyl or heterocylic groups R^5, R^6 and R^7 include those listed above for R^{22}, R^{23} and R^{24}.

[0020] Suitably R^1 is an optionally substituted phenyl, pyridyl, naphthyl, furyl or thienyl ring, and in particular is a substituted phenyl or pyridyl ring.

[0021] Suitable optional substitutents for R^1 in formula (I) include alkyl, alkenyl, alkynyl, halo, haloalkyl including perhaloalkyl such as trifluoromethyl, mercapto, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, hydroxyalkoxy, alkoxyalkoxy, alkanoyl, alkanoyloxy, cyano, nitro, amino, mono- or di-alkyl amino, oximino, sulphonamido, carbamoyl, mono or di-alkylcarbamoyl or $S(O)_m R^{26}$ where m is as defined above and R^{26} is hydrocarbyl.

[0022] Particular examples of substituents R^5, R^6 and R^7 include hydrogen, hydroxy, halo, optionally substituted alkyl such as aralkyl, carboxyalkyl or the amide derivative thereof; alkoxy; aryloxy; aralkyloxy; or an amino group which is optionally substituted with alkyl, aryl or aralkyl. A specific functional group which is suitable for R^5, R^6 and/or R^7 is a group of sub-formula (IV).



(IV)

[0023] Particular examples of groups R^5, R^6 and R^7 are hydrogen, hydroxy, halo or alkoxy. In particular R^6 and R^7 are hydrogen. R^5 may be hydrogen but in addition is suitably a small subsitutent such as hydroxy, halo or methoxy.

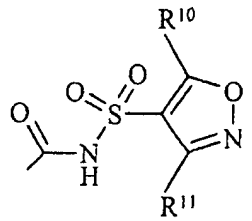
[0024] Particular substituents for R^1 include trifluoromethyl, C_{1-4}alkyl, halo, trifluoromethoxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, nitro, carbamoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, sulphonamido, carbamoylC_{1-4}alkyl, *N*-(C_{1-4}alkyl)carbamoylC_{1-4}alkyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl-C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

[0025] Additionally or alternatively, two such substituents together may form a divalent radical of the formula -O$(CH_2)_{1-4}$O- attached to adjacent carbon atoms on the R^1 ring.

[0026] Preferred substituents for R^1 are one or more non-polar substituents such as halo.

[0027] In particular, R^1 is substituted by one or more halo groups, in particular chlorine. A particular example of an R^1 group is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

[0028] Examples of groups R^2 include carboxy; cyano; tetrazol-5-yl; SO_3H; -CONHR^8 where R^8 is selected from cyano, hydroxy, -SO_2R^{12} where R^{12} is alkyl such as C_{1-4}alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R^8 is a group-$(CHR^{10})_r$-COOH where r is an integer of 1-3 and each R^{10} group is independently selected from hydrogen or alkyl such as C_{1-4} alkyl; or R^2 is a group -SO_2NHR^9 where R^9 is an optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl group, or a group COR^{14} where R^{14} is alkyl such as C_{1-4} alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R^2 is a group of formula (VI)



(VI)

where R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl.

[0029] Preferably R^2 is carboxy or a pharmaceutically acceptable salt or ester thereof.

[0030] Suitable groups R^3 include hydrogen, fluoro, chloro, bromo, iodo, methyl, cyano, trifluoromethyl, hydroxymethyl, alkoxyalkyl such as C_{1-4}alkoxymethyl, methoxy, benzyloxy, carboxyalkoxy such as carboxymethoxy, methylsulphanyl, methylsulphinyl, methylsulphonyl or carboxyC_{3-6}cycloalkyl, -$(CHR^{27})_r$-$NR^{28}R^{29}$ (where r is 0-2, each R^{27} is independently hydrogen or alkyl, in particular C_{1-4} alkyl, R^{28} and R^{29} are independently selected from H and C_{1-4}alkyl or R^{28} and R^{29} together with the nitrogen to which they are attached form a 5 or 6 membered ring optionally containing one further heteroatom selected from O, N, S, S(O) or SO_2. Suitably R^{28} and R^{29} together form a heterocylic ring such as morpholino or piperazinyl.

[0031] Other such groups R^3 include optionally substituted aryl groups, such as optionally substituted phenyl or naphthyl group. Suitable substituents for phenyl groups R^3 include one or more groups selected from chlorine, fluorine, methyl, trifluoromethyl, trifluoromethoxy, amino, formyl, phenyl, methoxy, phenoxy or phenyl.

[0032] R^3 may comprise a range of substituents as listed above, in particular, hydrogen or a small substituent group such as C_{1-4}alkyl in particular methyl, or trifluoromethyl, and is preferably hydrogen.

[0033] Suitable substitutents for hydrocarbyl and heterocyclic groups R^{15}, R^{16}, R^{18}, R^{19}, R^{20} and R^{21} as they appear in the definition of R^4 include those listed above in relation to R^{22}, R^{23} and R^{24}

[0034] Examples of R^4 are groups $C(O)NR^{15}R^{16}$ where one of R^{15} or R^{16} is hydrogen or alkyl such as methyl, and the other is optionally substituted heterocyclyl or optionally substituted alkyl such as C_{1-2} alkyl in particular methyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms. Suitable optional substitutents for heterocyclic groups R^{15} or R^{16} in this case are alkyl groups such as methyl, or oxo groups. Suitable optional substitutents for alkyl groups R^{15} and R^{16} include one or more groups selected from amino ; mono- or di-alkyl amino; carboxy; heterocyclyl optionally substituted with for example an alkyl groups such as methyl or an oxo group; or a group $NHSO_2R^{30}$ where R^{30} is alkyl such as methyl.

[0035] A preferred group for R^4 is a group $C(O)NR^{15}R^{16}$ where one of R^{15} or R^{16} is hydrogen and the other is heterocyclyl or alkyl substituted with one or more groups selected from amino, mono- or di-alkyl amino, carboxy or optionally substituted heterocyclyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms.

[0036] Where one of R^{15} or R^{16} is hydrogen, examples of suitable heterocyclyls for the other include imidazole, imidazolinone, or tetrahydrothiophene-1,1- dioxide.

[0037] Preferably one of R^{15} or R^{16} is hydrogen and the other is optionally substituted alkyl, for example C_{1-2} alkyl. Suitable substituents include one or more groups selected from amino, mono- or di-alkyl amino, a group $NHSO_2R^{30}$ where R^{30} is methyl, carboxy or optionally substituted heterocyclyl, such as isoxazole optionally substituted mono or di-substituted with alkyl, such as methyl.

[0038] Where R^{15} and R^{16} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms, that ring is, for example a morpholine ring. Alternatively, R^4 is a group of sub-formula (IV) as listed above.

[0039] Alternatively, R^4 is preferably a group $(CH_2)_t R^{17}$ where t is 1 and R^{17} is a group $NR^{18}R^{19}$. Particular examples of R^{18} and R^{19} include hydrogen and optionally substituted alkyl, or R^{18} and R^{19} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms, such as pyrazole or tetrahydropyranyl. In particular, R^{18} and R^{19} together form a morpholine ring.

[0040] X is CH_2 or SO_2 and is preferably CH_2.

[0041] Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

[0042] An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

[0043] Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, such as C_{1-6} alkyl esters for example, ethyl esters, C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

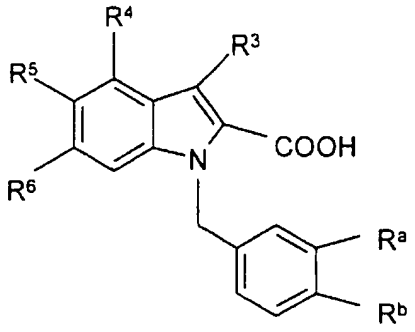
[0044] Suitable pharmaceutically acceptable esters of compounds of formula (I) are *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give

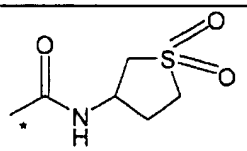
the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

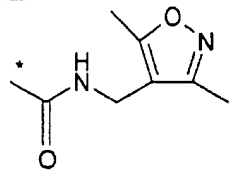
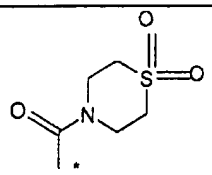
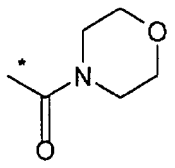
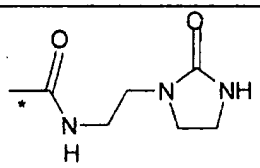
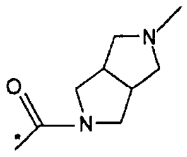
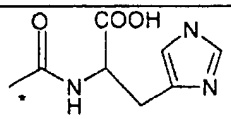
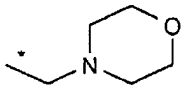
[0045] Esters which are not *in vivo* hydrolysable are useful as intermediates in the production of the compounds of formula (I) and therefore these form a further aspect of the invention.

[0046] Thus examples of compounds of formula (I) include the following:

Table 1



Compd No.	R^3	R^4	R^5	R^6	R^a	R^b
1	H		H	H	Cl	Cl

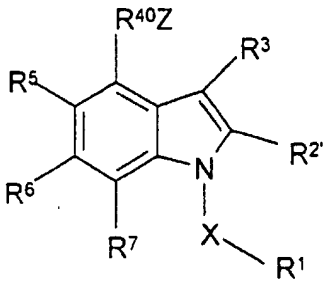
2	H		H	H	Cl	Cl
3	H		H	H	Cl	Cl
4	H		H	H	Cl	Cl
5	H	$CH_2N(CH_3)_2$	OH	H	Cl	Cl
6	H	$C(O)NH(CH_2)_2N(CH_3)_2$	H	H	Cl	Cl
7	H		H	H	Cl	Cl
8	H		H	H	Cl	Cl
9	H	$C(O)NH(CH_2)_2NHS(O)_2CH_3$	H	H	Cl	Cl
10	H		H	H	Cl	Cl
11	H		H	H	Cl	Cl

where * indicates the point of attachment of the group to the indole ring.

[0047] Yet a further aspect of the invention provides pharmaceutical compositions comprising a compound of formula (I) as defined above.

[0048] Compounds of formula (I) are suitably prepared by methods such as those described in International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341.

[0049] In particular compounds of formula (I) can be prepared by reacting a compound of formula (VII)



(VII)

where X, R^1, R^3, R^5, R^6 and R^7 are as defined in relation to formula (I) and $R^{2'}$ is a group R^2 as defined in relation to formula (I) or a protected form thereof, R^{40} is a group C(O) or a group $(CH_2)_t$ where t is as defined in relation to formula (I) and Z is a leaving group, either (a) when R^{40} is C(O), with a compound of formula (VIII)

$$HNR^{15}R^{16} \quad \text{(VIII)}$$

where R^{13} and R^{16} are as defined in relation to formula (I);
or (b) where R^{40} is group $(CH_2)_t$ with a compound of formula (IX)

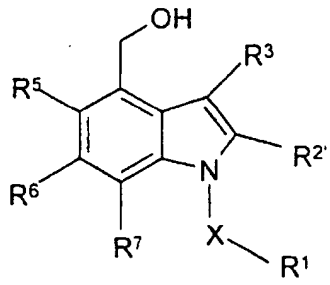
$$HR^{17} \quad \text{(IX)}$$

where R^{17} is as defined in relation to formula (I);
and thereafter if necessary or desirable, deprotecting a group $R^{2'}$ to a group R^2 or changing a group R^2 to a different such group.

[0050] Suitable leaving groups for Z include halo such as chloro. The reaction is suitably effected in an organic solvent such as dichloromethane or tetrahydrofuran in the presence of a base such as triethylamine. Moderate temperatures, for example of from 0° to 50°C and conveniently ambient temperature may be employed.

[0051] The compounds of formula (VII) suitably have an ester group as $R^{2'}$. Such compounds can then be converted to the corresponding acid by desterification, for example using sodium hydroxide in a mixture of methanol and tetrahydrofuran.

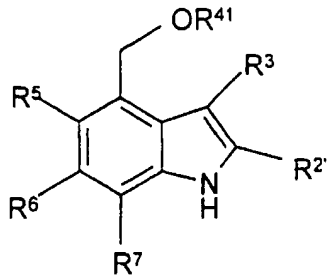
[0052] Compounds of formula (VII) where R^{40} is C(O) are suitably prepared in situ by reaction of the corresponding carboxylic acid with a halogenating agent such as oxalyl chloride. The acid is suitably derived from a compound of formula (X)



(X)

where X, R^1, $R^{2'}$, R^3, R^5, R^6 and R^7 are as defined above, by a sequence of reactions in which the hydroxy methyl group is first converted to a carboxaldehyde for example by reaction with 2,3-dichloro-5,6-dicyanobenzoquinone, which is then oxidised to the corresponding acid using conventional methods.

[0053] Compounds of formula (X) are suitably prepared by reacting a compound of formula (XI)



(XI)

where X, $R^{2'}$, R^3, R^5, R^6 and R^7 are as defined above and R^{41} is a protecting group, with a compound of formula (XII)

$$R^1\text{-}X\text{-}Z^1 \qquad \text{(XII)}$$

where R^1 and X are as defined in relation to formula (I) and Z^1 is a leaving group; and thereafter removing the protecting group R^{41}.

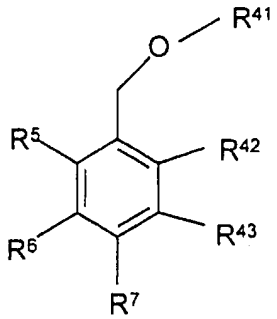
[0054] Suitable leaving groups for Z^1 include halide such as chloride, bromide or iodide, as well as mesylate or tosylate. The reaction is suitably effected in an organic solvent such as dimethylformamide (DMF) tetrahydrofuran (THF) or DCM in the presence of a base such as sodium hydride, sodium hydroxide, potassium carbonate. Optionally the reaction is effected in the presence of a suitable phase transfer catalyst. The choice of base and solvent is interdependent to a certain extent in that certain solvents are compatible with some bases only as is understood in the art. For example, sodium hydride may preferably be used with dimethylformamide or tetrahydrofuran and sodium hydroxide is preferably used with dichloromethane and a phase transfer catalyst.

[0055] The reaction can be carried out at moderate temperatures, for example from 0 to 50°C and conveniently at about ambient temperature.

[0056] Preferably, $R^{2'}$ is an ester group in the compound of formula IX and this may be subsequently converted to an acid or to another ester or salt, by conventional methods later in the process.

[0057] Suitable protecting groups R^{41} include acetyl, benzyl or tetrahydrpyranyl. The reaction conditions employed will be variable depending upon the nature of the protecting group R^{40} and would be apparent to a skilled person. Acetyl groups may be removed by reaction with a strong base such as sodium methoxide, whereas benzyl groups may be removed by hydrogenation, for example in the presence of a catalyst such as palladium catalyst. Removal of tetrahydropyranyl protecting groups may be effected using p-toluenesulphonic acid as illustrated hereinafter.

[0058] Compounds of formula (X) may be prepared by cyclisation of a compound of formula (XIII)

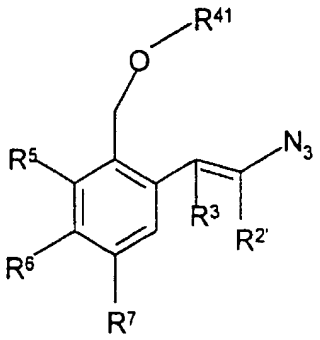


(XIII)

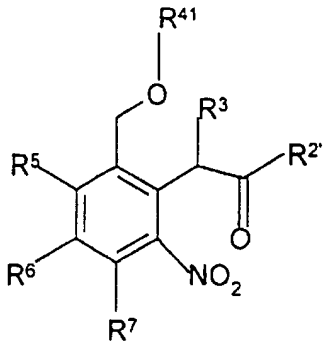
where R^5, R^6, R^7 and R^{41} are as defined above and R^{42} and R^{43} represent a combination of moieties which can cyclise to form an appropriately substituted pyrrole ring. For example, R^{42} can be a group of formula $-CH=C(R^{44})N_3$ where R^{44} is a group R^2 as defined above, or a protected form thereof, and R^{43} may be hydrogen. Cyclisation to form a compound of formula (XII) may then be effected by heating for example under reflux in an organic solvent, in particular a high boiling aprotic solvent such as xylene or toluene.

[0059] Alternatively, R^{43} may be nitro and R^{42} may be a group of formula $-CH_2C(O)R^{2'}$ where $R^{2'}$ is as defined above in relation to formula (VII). These compounds will cyclise in the presence of a catalyst such as palladium on carbon in the presence of hydrogen. The reaction may be effected at moderate temperatures for example of from 0 to 80°C, conveniently at about ambient temperature.

[0060] Thus examples of compounds of formula (XIII) include compounds of formula (XIV) and (XV)

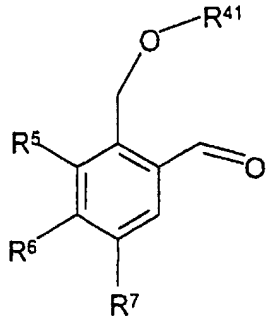


(XIV)



(XV)

[0061] Compounds of formula (XIII) where R^3 is hydrogen may be prepared for example by reacting a compound of formula (XVI)



(XVI)

with a compound of formula (XVII)

$$N_3CH_2R^{2'} \qquad \text{(XVII)}$$

where R^5, R^6, R^7, R^{41}, and $R^{2'}$ are as defined hereinbefore. The reaction may be effected in an organic solvent such as ethanol at low temperatures of from -20 to 0°C, suitably at about 0°C. The reaction is suitably effected in the presence of a base such as an alkoxide, in particular an ethoxide, for example potassium ethoxide.

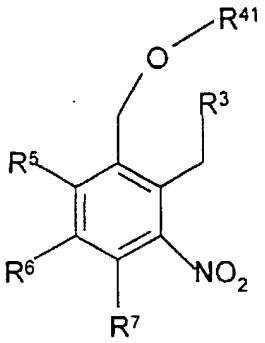
[0062] Where necessary or desired, R^3 can be converted from hydrogen to a different group R^3 subsequently in the reaction scheme, using conventional methods.

[0063] Compounds of formula (XVII) are suitably prepared by reacting a compound of formula (XVIII)

$$R^{47}CH_2R^{2'} \qquad \text{(XVIII)}$$

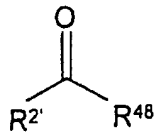
where $R^{2'}$ is as defined above and R^{47} is a leaving group such as halide and in particular bromide, with an azide salt, such as an alkali metal azide salt in particular sodium azide.

[0064] Compounds of formula (XV) may be prepared by reacting a compound of formula (XIX)



(XIX)

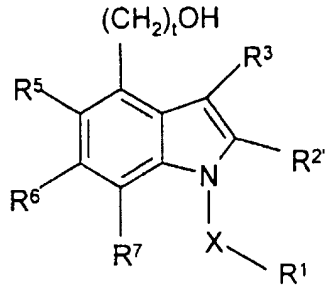
where R^5, R^6, R^7, R^3, R^{40} and $R^{2'}$ are as defined above, with a compound of formula (XX)



(XX)

where $R^{2'}$ is as defined above and R^{48} leaving group such as hydroxy. Examples of compounds of formula (XX) are oxalates such as diethyloxalate. The reaction is suitably effected in the presence of a base such as sodium hydride in an organic solvent such as THF. Moderate temperatures of from 0° to 40°C and conveniently ambient temperature is employed.

[0065] Compounds of formula (VII) where R^{40} is $(CH_2)_t$ may be prepared by halogenation of a compound of formula (XXI)



(XXI)

where t, R^1, $R^{2'}$, R^3, R^5, R^6 and R^7 are as defined above. Compound (X) above is a particular example of a compound of formula (XXI) and others may be prepared by analogous methods to those described for formula (X).

[0066] Compounds of formula (XI), (XVI), (XVII), (XVIII), (XIX) and (XX) are either known compounds or they can be prepared from known compounds by conventional methods.

[0067] According to a further aspect of the invention there is provided a compound of the formula **(I)** as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of inflammatory disease.

[0068] According to a further aspect of the present invention there is provided a method for antagonising an MCP-1 mediated effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula **(I),** or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

[0069] The invention also provides a compound of formula **(I)** as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, for use as a medicament.

[0070] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

[0071] The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[0072] Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate,

stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

[0073] Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

[0074] Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

[0075] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0076] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

[0077] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

[0078] Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

[0079] The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

[0080] Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

[0081] Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

[0082] Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

[0083] Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

[0084] For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[0085] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[0086] The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of rats.

[0087] In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example. 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

[0088] The invention is further illustrated, but not limited by the following Examples in which the following general procedures were used unless stated otherwise.

Preparation 1

Ethyl *N*-(3,4-dichlorobenzyl)-4-(2-tetrahydropyranyloxy)methylindole-2-carboxylate

[0089] Ethyl-4-(2-tetrahydropyranyloxy)methylindole-2-carboxylate (5.1 g) (Chung-gi Shen et al., Heterocycles, 43, 1996, 891-898) and sodium hydride (741 mg, 60% in mineral oil) were stirred in DMF (100 ml) under argon at ambient temperature for 20 minutes. 3,4-Dichlorobenzyl chloride (2.79 ml) was added and the mixture stirred overnight, then partitioned between ethyl acetate (150 ml) and water (150 ml). The organic phase was washed with water (2 x 150 ml), dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography using *iso*-hexane, then ethyl acetate : *iso*-hexane (5/95) as eluent to give the product as a yellow oil (4.39 g, 56%); NMR δ ($CDCl_3$) 1.40 (t, 3H), 1.50 - 2.00 (m. 6H), 3.60 (m, 1H), 4.00 (m, 1H), 4.35 (q, 2H), 4.75 (m, 1H), 4.85 (d, 1H), 5.10 (d, 1H), 5.80 (s, 2H), 6.85 (m,1H), 7.15 - 7.40 (m, 5H), 7.50 (s, 1H); *M*/z (+) 462.5 (MH^+).

Preparation 2

Ethyl *N*-(3,4-dichlorobenzyl)-4-hydroxymethylindole-2-carboxylate

[0090] Ethyl *N*-(3,4-dichlorobenzyl)-4-(2-tetrahydropyranyloxy)methylindole-2-carboxylate (4.38 g) and *p*-toluenesulphonic acid (100 mg) in ethanol (100 ml) was stirred at ambient temperature for 3 hours, then concentrated *in vacuo* and the residue dissolved in ethyl acetate (100 ml), washed with water (100 ml), dried ($MgSO_4$) and concentrated to give the product as an off-white solid (3.22 g, 90%); NMR δ (CD_3SOCD_3) 1.25 (t, 3H), 4.25 (q, 2H), 4.80 (d, 2H), 5.20 (m, 1H), 5.80 (s, 2H), 6.85 (m,1H), 7.10 (d, 1H), 7.30 (m, 2H), 7.50 (m, 3H); *M*/z (+) 378.3 (MH^+).

Preparation 3

Ethyl 4-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate

[0091] Ethyl *N*-(3,4-dichlorobenzyl)-4-hydroxymethylindole-2-carboxylate (5.17 g) and 2,3-dichloro-5,6-dicyanobenzoquinone (3.10 g) were stirred in dioxane (100 ml) at ambient temperature, overnight. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 ml) and filtered. The filtrate was concentrated *in vacuo* and the residue purified by column chromatography using 10% ethyl acetate : *iso*-hexane as eluent to give product as a yellow solid (4.88 g, 95%); NMR δ (CD_3SOCD_3) 1.30 (t, 3H), 4.30 (q, 2H), 5.90 (s, 2H), 6.85 (m,1H), 7.90 (m, 1H), 8.00 (m, 1H), 10.22 (s, 1H); *M*/z(+) 376.3 (MH^+).

Preparation 4

***N*-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-4-carboxylic acid**

[0092] A solution of sodium chlorite (9.70 g) and sodium dihydrogen orthophosphate (13.02 g) in water (50 ml) was added dropwise to a solution of ethyl 4-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (4.47 g) and 2-methylbut-2-ene (50 ml) in *tert*-butyl alcohol (100 ml) and the mixture stirred for 72 hours at ambient temperature, then concentrated *in vacuo* and the resulting precipitate was filtered and dried to give the product as an off-white solid (4.16 g, 89%); NMR δ (CD_3SOCD_3) 1.25 (t, 3H), 4.30 (q, 2H), 5.85 (s, 2H), 6.85 (m,1H), 7.35 (m, 1H), 7.40 (q, 1H), 7.50 (m, 1H), 7.80 (m, 3H); *M*/z(-) 390.1 (*M*-H$^+$).

Preparation 5

Ethyl 4-chloromethyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate

[0093] Ethyl *N*-(3,4-dichlorobenzyl)-4-hydroxymethylindole-2-carboxylate (0.89 g), dimethylformamide (0.5 ml) and thionyl chloride (189 µl) in dichloromethane (40 ml) were stirred at ambient temperature overnight and the resulting precipitate was filtered and dried *in vacuo* to give the product as a white solid (0.62 g, 67%); NMR δ (CD_3SOCD_3) 1.30 (t, 3H), 4.30 (q, 2H), 5.10 (s, 2H), 5.85 (s, 2H), 6.90 (m, 1H), 7.30 (m, 3H), 7.55 (m. 3H); *M*/z (+) 396.2 (*M*H$^+$).

Preparation 6

Ethyl 5-hydroxyindole-2-carboxylate

[0094] Boron tribromide (64.58 g) was added dropwise to a stirred solution of ethyl 5-methoxyindole-2-carboxylate (20 g) in dry dichloromethane (1000 ml) at -78°C under an atmosphere of argon. The reaction was allowed to warm to room temperature and stirred for a further 2 hours. The reaction was poured into ice / saturated aqueous sodium hydrogen carbonate solution with stirring and extracted with ethyl acetate. Combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water, aqueous saturated sodium chloride solution and dried ($MgSO_4$). The solution was concentrated *in vacuo* and the residue was purified by column chromatography using 0 - 60% diethyl ether ; *iso*-hexane as eluent to give product as a white solid (9.02 g, 48%); NMR δ (CD_3SOCD_3) 1.31 (t, 3H), 4.29 (q, 2H), 6.79 (dd, 1H), 6.90 (dd, 1H), 7.22 (d, 1H), 8.84 (s, 1H), 11.52 (brs, 1H); *M*/z(+) 206 (*M*H$^+$).

Preparation 7

Ethyl 5-acetoxyindole-2-carboxylate

[0095] A stirred solution of ethyl 5-hydroxyindole-2-carboxylate (7.79 g) and DMAP (20 mg) in acetic anhydride (80 ml) was heated at 80°C for 4 hours. The reaction was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. Combined organic extracts were washed with hydrochloric acid (2.0 M), saturated aqueous sodium hydrogen carbonate solution, water, aqueous saturated sodium chloride solution and dried ($MgSO_4$). The solution was concentrated *in vacuo* to give the product as a yellow solid (9.39 g,100 %): NMR δ (CD_3SOCD_3) 1.20 (t, 3H), 2.10 (s, 3H), 4.19 (q, 2H), 6.86 (dd, 1H), 6.97 (d, 1H), 7.20 (s, 1H), 7.29 (d, 1H); *M*/z (+) 248 (*M*H$^+$).

Preparation 8

Ethyl 5-acetoxy-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate

[0096] 3,4-Dichlorobenzyl bromide (5.96 g) was added to a stirred solution of ethyl 5-acetoxyindole-2-carboxylate (5.4 g) and potassium carbonate (6.94 g) in acetonitrile (500 ml) under an atmosphere of argon. The reaction was heated at 80°C for 16 hours, then concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. Combined organic extracts were washed with water, saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was triturated with *iso*-hexane to give the product as a cream solid (5.55 g, 63%); NMR δ (CD_3SOCD_3) 1.27 (t, 3H), 2.27 (s, 3H), 4.28 (q, 2H), 5.82 (s, 2H), 6.90 (d, 1H), 7.09 (dd, 1H), 7.33 - 7.40 (m, 2H), 7.46 (d, 1H) 7.52 (d, 1H), 7.60 (d, 1H).

Preparation 9

Ethyl *N*-(3,4-dichlorobenzyl)-5-hydroxyindole-2-carboxylate

[0097] Sodium ethoxide (1.86 g) was added to a stirred solution of ethyl 5-acetoxy-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (5.55 g) in ethanol (50 ml) under an atmosphere of argon. The reaction was stirred at room temperature for 2 hours, then concentrated *in vacuo* and the residue acidified with aqueous hydrochloric acid (2.0 M) and extracted with dichloromethane. Combined organic extracts were washed with water, saturated aqueous sodium chloride solution and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was triturated with hexane / diethyl ether to give the product as a white solid (3.17 g, 92%); NMR δ (CD_3SOCD_3) 1.26 (t, 3H), 4.25 (q, 2H), 5.75 (s, 2H), 6.81 - 6.91 (m, 2H), 6.98 (d, 1H), 7.19 (s, 1H), 7.29 (d, 1H), 7.38 (d, 1H) 7.50 (d, 1H), 9.06 (s, 1H); *M*/z(+) 364 (*M*H$^+$).

Example 1

Compound 1 ethyl ester

[0098] *N*-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-4-carboxylic acid (100 mg), DMF (1 drop) and a solution of oxalyl chloride in dichloromethane (2M, 140 µl) were stirred in dichloromethane (4 ml) under argon, at ambient temperature, for 7 hours. The reaction mixture was concentrated *in vacuo* and dissolved in dichloromethane (4 ml). 3-amino-tetrahydrothiophene-1,1-dioxide (69 mg) and triethylamine (71 µl) were added and the reaction stirred under argon, overnight. The reaction mixture was diluted with dichloromethane (20 ml), washed with aq. 2M HCl (30 ml) and water (30 ml), dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography using ethyl acetate : *iso*-hexane (gradient 25/75-100/0) as eluent to give the product as an off-white solid (73 mg, 56%). *M*/z(+) 509.3 (*M*H$^+$).

Example 2

[0099] The procedure described in Example 1 above was repeated using the appropriate amine. Thus were obtained the compounds described below.

Compound 4 ethyl ester

[0100] 48% yield; *M*/z (+) 461.5 (*M*H$^+$).

Compound 2 ethyl ester

[0101] 96% yield; *M*/z (+) 500.4 (*M*H$^+$).

Compound 3 ethyl ester

[0102] 60% yield; *M*/z (+) 509.3 (*M*H$^+$).

Compound 6 ethyl ester

[0103] 63% yield; *M*/z (+) 462.2 (*M*H$^+$).

Compound 7 ethyl ester

[0104] 72% yield; *M*/z(+) 503.2 (*M*H$^+$).

Compound 8 ethyl ester

[0105] 51% yield; *M*/z(+) 500.2 (*M*H$^+$).

Compound 9 ethyl ester

[0106] 13% yield; *M*/z (+) 512.1 (*M*H$^+$).

Example 3

Compound 10 ethyl methyl diester

[0107] *N*-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-4-carboxylic acid (150 mg), *L*-histidine methyl ester dihydrochloride (93 mg), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (123 mg) and triethylamine (107 µl) were stirred in dichloromethane (15 ml) at ambient temperature, overnight. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography using ethyl acetate ; *iso*-hexane (gradient 10/90 - 100/0) then 10% methanol : ethyl acetate as eluent to give product as a white gum (35 mg, 17%); *M*/z(+) 543.2 (MH$^+$).

Example 4

Compound 4

[0108] Compound 4 ethyl ester (50 mg) was dissolved in tetrahydrofuran (2 ml). Aqueous sodium hydroxide (2M, 2 ml) and methanol (1 ml) were added and the mixture stirred at ambient temperature for 2 hours, then concentrated *in vacuo* and the residue dissolved in water (4 ml), acidified with acetic acid and resulting precipitate filtered, washed with water and dried *in vacuo* to give the product as a white solid (19mg, 40%); NMR δ (CD_3SOCD_3) 3.30 - 3.90 (m, 8H), 6.00 (s, 2H), 7.05 (m, 1H), 7.20 (m, 2H), 7.40 (t, 1H), 7.50 (m, 1H), 7.60 (m, 1H), 7.70 (m, 1H); *M*/z (-) 431.4 (M-H$^-$).

Example 5

[0109] The procedure described in Example 4 above was repeated using the appropriate ester. Thus were obtained the compounds described below.

Compound 1

[0110] 77% yield; NMR δ (CD_3SOCD_3) 2.20 (m, 1H), 3.05 - 3.60 (m, 5H), 4.70 (m, 1H), 5.90 (s, 2H), 6.90 (m, 1H), 7.30 (m, 2H), 7.50 (m, 2H), 7.60 (s, 1H), 7.70 (m, 1H), 8.70 (d, 1H); *M*/z(-) 481.3 (M-H$^-$).

Compound 2

[0111] 90% yield; NMR δ (CD_3SOCD_3) 2.20 (s, 3H), 2.40 (s, 3H), 4.20 (d, 2H), 6.00 (s, 2H), 7.00 (m, 1H), 7.20 (t, 1H), 7.35 (m, 3H), 7.50 (m, 1H), 7.55 (m. 1H), 8.60 (t, 1H); *M*/z (-) 470.1 (M-H$^-$).

Compound 3

[0112] 53% yield; *M*/z (-) 479.1 (M-H$^-$).

Compound 6

[0113] 81% yield; NMR δ (CD_3SOCD_3) 2.40 (m, 6H), 2.75 (m, 2H), 3.45 (m, 2H), 5.85 (s, 2H), 6.85 (m, 1H), 7.25 (m, 2H), 7.45 (m, 2H), 7.60 (m, 2H), 8.35 (m, 1H); *M*/z (-) 432.2 (M-H$^-$).

Compound 7

[0114] 98% yield; NMR δ (CD_3SOCD_3) 3.22 (m, 2H), 3.40 (m, 2H), 5.90 (s, 2H), 6.23 (s, 1H), 6.90 (m, 1H), 7.30 (m, 2H), 7.50 (m, 2H), 7.65 (m, 2H), 8.40 (m, 1H); *M*/z (-) 473.2 (M-H$^-$).

Compound 8

[0115] 100% yield; *M*/z (-) 470.2 (M-H$^-$).

Compound 9

[0116] 85% yield; NMR δ (CD_3SOCD_3) 2.90 (s, 3H), 3.15 (m, 2H), 3.40 (m, 2H), 5.95 (s, 2H), 6.90 (m, 1H), 7.15 (m, 1H), 7.30 (m, 2H), 7.50 (m, 2H), 7.60 (m, 1H), 7.65 (m, 1H), 8.40 (m, 1H); *M*/z (-) 482.4 (M-H$^-$).

Compound 10

[0117] 51% yield; *M*/z(-) 499.1 (*M*-H$^-$).

Compound 11

[0118] 50% yield; NMR δ (CD_3SOCD_3) 2.40 (m, 4H), 3.50 (m, 4H), 3.70 (s, 2H), 5.85 (s, 2H), 6.90 (m, 1H), 7.05 (m, 1H), 7.20 (m, 1H), 7.30 - 7.60 (m, 4H); *M*/z (-) 417.2 (*M*-H$^-$).

Example 6

Compound 11 ethyl ester

[0119] Ethyl 4-chloromethyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (150 mg), morpholine (50 µl) and triethylamine (106 µl) in tetrahydrofuran (5 ml) were stirred at ambient temperature for 4 days, then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (30 ml), washed with water (30 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was triturated with toluene and the resulting white solid filtered and dried (79 mg, 47%); NMR δ ($CDCl_3$) 1.42 (t, 3H), 2.98 (m, 2H), 3.37 (m, 2H), 3.95 (m, 2H), 4.20-4.60 (m, 6H), 5.80 (s, 2H), 6.90 (m, 1H), 7.20 (m, 1H), 7.25 - 7.60(m, 4H), 7.70 (m,1H); *M*/z (+) 447.3 (*M*H$^+$).

Example 7

Ethyl *N*-(3,4-dichlorobenzyl)-4-dimethylaminomethyl-5-hydroxyindole-2-carboxylate (Ethyl ester of Compound 5)

[0120] To a stirred solution of ethyl *N*-(3,4-dichlorobenzyl)-5-hydroxyindole-2-carboxylate (2.1 g) in ethanol (50 ml) was added successively aqueous dimethylamine (40%, 0.5 ml) and aqueous formaldehyde (0.5 ml). The solution was allowed to stand overnight and the resulting crystals filtered and dried *in vacuo* to give the product as pale yellow crystals (1.7 g, 70%); NMR δ (CD_3SOCD_3) 1.24 (t, 3H), 2.23 (s, 6H), 3.81 (s, 2H), 4.24 (q, 2H), 5.75 (s, 2H), 6.82 (d, 1H), 6.90 (dd, 1H), 7.30 (m, 3H), 7.50 (d, 1H); *M*/z(+) 423, 421 (*M*H$^+$), 378, 376.

Example 8

***N*-(3,4-Dichlorobenzyl)-4-dimethylaminomethyl-5-hydroxyindole-2-carboxylic acid (Compound 5)**

[0121] Using the method of Example 5, the ester from Example 7 was converted to the title compound.
72% yield; NMR δ (CD_3SOCD_3) 2.43 (s, 6H), 4.04 (s, 2H), 5.85 (s, 2H), 6.78 (d, 1H), 7.00 (dd, 1H), 7.18 (s, 1H), 7.22 (d, 1H), 7.34 (s, 1H), 7.42 (d, 1H); *M*/z (+) 393, 391 (*M*H$^+$), 348, 347.

Example 9

Biological Assays for hMCP-1 Antagonists

Biological Testing.

[0122] The following biological test methods, data and Examples serve to illustrate the present invention.

Abbreviations:

[0123]

ATCC	American Type Culture Collection, Rockville, USA.
BCA	Bicinchroninic acid, (used, with copper sulphate, to assay protein)
BSA	Bovine Serum Albumin
DMEM	Dulbecco's modified Eagle's medium
EGTA	Ethylenebis(oxyethylenenitrilo)tetraacetic acid
FCS	Foetal calf serum
HEPES	(N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid])

HBSS	Hank's Balanced Salt Solution
hMCP-1	Human Monocyte Chemoattractant Protein-1
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction

[0124] AMPLITAQ™, available from Perkin-Elmer Cetus, is used as the source of thermostable DNA polymerase.

[0125] Binding Buffer is 50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% foetal calf serum, adjusted to pH 7.2 with 1 M NaOH.

[0126] Non-Essential Amino Acids (100X concentrate) is: L-Alanine, 890 mg/l; L-Asparagine, 1320 mg/l; L-Aspartic acid, 1330 mg/l; L-Glutamic acid, 1470 mg/l; Glycine, 750 mg/l; L-Proline, 1150 mg/l and; L-Serine, 1050 mg/l.

[0127] Hypoxanthine and Thymidine Supplement (50x concentrate) is: hypoxanthine, 680 mg/l and; thymidine, 194 mg/l.

[0128] Penicillin-Streptomycin is: Penicillin G (sodium salt); 5000 units/ml; Streptomycin sulphate, 5000 µg/ml.

[0129] Human monocytic cell line THP-1 cells are available from ATCC, accession number ATCC TIB-202.

[0130] Hank's Balanced Salt Solution (HBSS) was obtained from Gibco; see *Proc. Soc. Exp. Biol. Med.*, 1949, **71,** 196.

[0131] Synthetic cell culture medium. RPMI 1640 was obtained from Gibco; it contains inorganic salts [$Ca(NO_3)_2$. $4H_2O$ 100 mg/l; KCl 400 mg/l; $MgSO_4.7H_2O$ 100 mg/l; NaCl 6000 mg/l; $NaHCO_3$ 2000 mg/l & Na_2HPO_4 (anhyd) 800 mg/l], D-Glucose 2000 mg/l, reduced glutathione 1 mg/l, amino acids and vitamins.

[0132] FURA-2/AM is 1-[2-(5-carboxyoxazol-2-yl)-6-aminobenzofuran-5-oxy]-2-(2'-amino-5'-methylphenoxy)-ethane-*N,N,N',N'*-tetraacetic acid pentaacetoxymethyl ester and was obtained from Molecular Probes, Eugene, Oregon, USA.

[0133] Blood Sedimentation Buffer contains 8.5g/l NaCl and 10g/l hydroxyethyl cellulose.

[0134] Lysis Buffer is 0.15M NH_4Cl, 10mM $KHCO_3$, 1mM EDTA

[0135] Whole Cell Binding Buffer is 50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA, 0.01% NaN_3, adjusted to pH 7.2 with 1M NaOH.

[0136] Wash buffer is 50mM HEPES. 1mM $CaCl_2$, 5mM $MgCl_2$, 0.5% heat inactivated FCS, 0.5MNaCl adjusted to pH7.2 with 1M NaOH.

[0137] General molecular biology procedures can be followed from any of the methods described in "Molecular Cloning - A Laboratory Manual" Second Edition, Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory, 1989).

i) Cloning and expression of hMCP-1 receptor

[0138] The MCP-1 receptor B (CCR2B) cDNA was cloned by PCR from THP-1 cell RNA using suitable oligonucleotide primers based on the published MCP-1 receptor sequences (Charo *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, **91,** 2752). The resulting PCR products were cloned into vector PCR-II™ (InVitrogen, San Diego, CA.). Error free CCR2B cDNA was subcloned as a Hind III-Not I fragment into the eukaryotic expression vector pCDNA3 (InVitrogen) to generate pCDNA3/CC-CKR2A and pCDNA3/CCR2B respectively.

[0139] Linearised pCDNA3/CCR2B DNA was transfected into CHO-K1 cells by calcium phosphate precipitation (Wigler *et al.*, 1979, *Cell,* **16,** 777). Transfected cells were selected by the addition of Geneticin Sulphate (G418, Gibco BRL) at 1mg/ml, 24 hours after the cells had been transfected. Preparation of RNA and Northern blotting were carried out as described previously (Needham *et al.*, 1995, *Prot. Express. Purific.*, **6,** 134). CHO-K1 clone 7 (CHO-CCR2B) was identified as the highest MCP-1 receptor B expressor.

ii) Preparation of membrane fragments

[0140] CHO-CCR2B cells were grown in DMEM supplemented with 10% foetal calf serum, 2 mM glutamine, 1x Non-Essential Amino Acids, 1x Hypoxanthine and Thymidine Supplement and Penicillin-Streptomycin (at 50 µg streptomycin/ml, Gibco BRL). Membrane fragments were prepared using cell lysis/differential centrifugation methods as described previously (Siciliano *et al.*, 1990, *J. Biol. Chem.*, **265,** 19658). Protein concentration was estimated by BCA protein assay (Pierce, Rockford, Illinois) according to the manufacturer's instructions.

iii) Assay

[0141] ^{125}I MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133,** 529; Amersham International plc]. Equilibrium binding assays were carried out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152,** 3541. Briefly, varying amounts of ^{125}I-labeled MCP-1 were added to 7µg of purified CHO-CCR2B cell membranes in 100 µl of Binding Buffer. After 1 hour incubation at room temperature the binding reaction mixtures were

filtered and washed 5 times through a plate washer (Brandel MLR-96T Cell Harvester) using ice cold Binding Buffer. Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 0.3% polyethylenimine prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound ^{125}I-labeled MCP-1 was determined (LKB 1277 Gammamaster). Cold competition studies were performed as above using 100 pM ^{125}I-labeled MCP-1 in the presence of varying concentrations of unlabelled MCP-1. Non-specific binding was determined by the inclusion of a 200-fold molar excess of unlabelled MCP-1 in the reaction.

[0142] Ligand binding studies with membrane fragments prepared from CHO-CCR2B cells showed that the CCR2B receptor was present at a concentration of 0.2 pmoles/mg of membrane protein and bound MCP-1 selectively and with high affinity (IC_{50} = 110 pM, K_d =120 pM). Binding to these membranes was completely reversible and reached equilibrium after 45 minutes at room temperature, and there was a linear relationship between MCP-1 binding and CHO-CCR2B cell membrane concentration when using MCP-1 at concentrations between 100 pM and 500 pM.

[0143] Test compounds dissolved in DMSO (5µl) were tested in competition with 100 pM labelled MCP-1 over a concentration range (0.01-50µM) in duplicate using eight point dose-response curves and IC_{50} concentrations were calculated.

[0144] Compounds tested of the present invention had IC_{50} values of 50µM or less in the hMCP-1 receptor binding assay described herein.

b) MCP-1 mediated calcium flux in THP-1 cells

[0145] The human monocytic cell line THP-1 was grown in a synthetic cell culture medium RPMI 1640 supplemented with 10 % foetal calf serum, 6mM glutamine and Penicillin-Streptomycin (at 50 µg streptomycin/ml, Gibco BRL). THP-1 cells were washed in HBSS (lacking Ca^{2+} and Mg^{2+}) + 1 mg/ml BSA and resuspended in the same buffer at a density of 3 x 10^6 cells/ml. The cells were then loaded with 1mM FURA-2/AM for 30 min at 37°C, washed twice in HBSS, and resuspended at 1x10^6 cells/ml. THP-1 cell suspension (0.9 ml) was added to a 5 ml disposable cuvette containing a magnetic stirrer bar and 2.1 ml of prewarmed (37°C) HBSS containing 1 mg/ml BSA, 1 mM $MgCl_2$ and 2 mM $CaCl_2$. The cuvette was placed in a fluorescence spectrophotometer (Perkin Elmer, Norwalk, CT) and preincubated for 4 min at 37°C with stirring. Fluorescence was recorded over 70 sec and cells were stimulated by addition of hMCP-1 to the cuvette after 10 sec. $[Ca^{2+}]i$ was measured by excitation at 340 nm and 380 nm alternately and subsequent measurement of the intensity of the fluorescence emission at 510 nm. The ratio of the intensities of the emitted fluorescent light following excitation at 340 nm and 380 nm, (R), was calculated and displayed to give and estimate of cytoplasmic $[Ca^{2+}]$ according to the equation:-

$$[Ca^{2+}]i = K_d \frac{(R-Rmin)}{(Rmax-R)} (Sf2/Sb2)$$

where the K_d for FURA-2 Ca^{2+} complex at 37°C was taken to be 224nm. R_{max} is the maximal fluorescence ratio determined after addition of 10 mM Ionomycin, R_{min} is the minimal ratio determined by the subsequent addition of a Ca^{2+} free solution containing 5 mM EGTA, and Sf2/Sb2 is the ratio of fluorescence values at 380 nm excitation determined at R_{min} and R_{max}, respectively.

[0146] Stimulation of THP-1 cells with hMCP-1 induced a rapid, transient rise in $[Ca^{2+}]_i$ in a specific and dose dependent manner. Dose response curves indicated an approximate EC_{50} of 2 nm. Test compounds dissolved in DMSO (10µl) were assayed for inhibition of calcium release by adding them to the cell suspension 10 sec prior to ligand addition and measuring the reduction in the transient rise in $[Ca^{2+}]i$. Test compounds were also checked for lack of agonist activity by addition in place of hMCP-1.

c) hMCP-1 and RANTES mediated chemotaxis.

[0147] *In vitro* chemotaxis assays were performed using the human monocytic cell line THP-1. Cell migration through polycarbonate membranes was measured by enumerating those passing through either directly by Coulter counting or indirectly by use of a colourimetric viability assay measuring the cleavage of a tetrazolium salt by the mitochondrial respiratory chain (Scudiero D.A. *et al.* 1988, *Cancer Res.*, **48,** 4827-4833).

[0148] Chemoattractants were introduced into a 96-well microtitre plate which forms the lower well of a chemotaxis chamber fitted with a PVP-free 5 µm poresize polycarbonate adhesive framed filter membrane (NeuroProbe MB series, Cabin John, MD 20818, USA) according to the manufacturer's instructions. The chemoattractant was diluted as appropriate in synthetic cell culture medium, RPMI 1640 (Gibco) or supplemented with 2 mM glutamine and 0.5% BSA, or alternatively with HBSS with Ca^{2+} and Mg^{2+} without Phenol Red (Gibco) plus 0.1% BSA. Each dilution was degassed under vacuum for 30 min and was placed (400 µl) in the lower wells of the chamber and THP-1 cells (5x10^5 in 100 µl RPMI 1640 + 0.5%BSA) were incubated in each well of the upper chamber. For the inhibition of chemotaxis the che-

moattractant was kept at a constant submaximal concentration determined previously (1nM MCP-1) and added to the lower well together with the test compounds dissolved in DMSO (final DMSO concentration < 0.05% v/v) at varying concentrations. The chamber was incubated for 2 h at 37°C under 5 % CO_2. The medium was removed from the upper wells which were then washed out with 200 µl physiological saline before opening the chamber, wiping dry the membrane surface and centrifuging the 96-well plate at 600 g for 5 min to harvest the cells. Supernatant (150 µl) was aspirated and 10 µl of cell proliferation reagent, WST-1, {4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-phenyl disulfonate} plus an electron coupling reagent (Boehringer Mannheim, Cat.no. 1644 807) was added back to the wells. The plate was incubated at 37°C for 3 h and the absorbance of the soluble formazan product was read on a microtitre plate reader at 450 nm. The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average absorbance values, standard error of the mean, and significance tests were calculated. hMCP-1 induced concentration dependent cell migration with a characteristic biphasic response, maximal 0.5-1.0 nm.

[0149] In an alternative form of the above assay, fluorescently tagged cells can be used in order to assist in end point detection. In this case, the THP-1 cells used are fluorescently tagged by incubation in the presence of 5mM Calcein AM (Glycine, N,N'-[[3',6'-bis(acetyloxy)-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthene]-2',7'-diyl]bis(methylene)] bis [N-[2-[(acetyloxy)methoxy]-2-oxoethyl]]-bis[(acetyloxy)methyl] ester; Molecular Probes) for 45 minutes in the dark. Cells are harvested by centrifugation and resuspended in HBSS (without Phenol Red) with Ca^{2+}, Mg^{2+} and 0.1% BSA. 50µl (2x105 cells) of the cell suspension are placed on the filter above each well and, as above, the unit is incubated at 37°C for 2 hours under 5% CO_2. At the end of the incubation, cells are washed off the upper face of the filter with phosphate buffered saline, the filter removed from the plate and the number of cells attracted to either the underside of the filter or the lower well estimated by reading fluorescence at 485nm excitation, 538nm emission wavelengths (fmax, Molecular Devices). The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average fluorescence values, standard error of the mean, percentage inhibition and IC_{50} of compounds under test and significance tests can be calculated. In addition to MCP-1 induced chemotaxis, this alternative form of the assay was also used to measure inhibition of RANTES (2nM) induced chemotaxis.

d) Binding to human peripheral blood mononuclear cells(PBMCs)

i) Preparation of human PBMCs

[0150] Fresh human blood (200ml) was obtained from volunteer donors, collected into sodium citrate anticoagulant to give a final concentration of 0.38%. The blood was mixed with Sedimentation Buffer and incubated at 37°C for 20 minutes. The supernatant was collected and centrifuged at 1700rpm for 5 minutes (Sorvall RT6000D). The pellet obtained was resuspended in 20 ml RPMI/BSA (1mg/ml) and 4 x 5mls of cells were carefully layered over 4 x 5mls of Lymphoprepä (Nycomed) in 15ml centrifuge tubes. Tubes were spun at 1700rpm for 30 minutes (Sorvall RT6000D) and the resultant layer of cells was removed and transferred to 50ml Falcon tubes. The cells were washed twice in Lysis Buffer to remove any remaining red blood cells followed by 2 washes in RPMI/BSA. Cells were resuspended in 5mls of Binding Buffer. Cell number was measured on a Coulter counter and additional binding buffer was added to give a final concentration of 1.25x 10^7 PBMCs /ml.

ii) Assay

[0151] [^{125}I]MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133,** 529; Amersham International plc]. Equilibrium binding assays were carried out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152,** 3541. Briefly, 50µl of ^{125}I-labeled MCP-1 (final concentration 100pM) was added to 40µl (5x10^5 cells) of cell suspension in a 96 well plate. Compounds, diluted in Whole Cell Binding Buffer from a stock solution of 10mM in DMSO were added in a final volume of 5µl to maintain a constant DMSO concentration in the assay of 5%. Total binding was determined in the absence of compound. Non-specific binding was defined by the addition of 5µl cold MCP-1 to give a final assay concentration of 100nM. Assay wells were made up to a final volume of 100µl with Whole Cell Binding Buffer and the plates sealed. Following incubation at 37°C for 60 minutes the binding reaction mixtures were filtered and washed for 10 seconds using ice cold Wash Buffer using a plate washer (Brandel MLR-96T Cell Harvester). Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 0.3% polyethylenimine plus 0.2% BSA prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound ^{125}I-labeled MCP-1 was determined (LKB 1277 Gammamaster).

[0152] Test compound potency was determined by assay in duplicate using six point dose-response curves and IC_{50} concentrations were determined.

[0153] Compounds tested of the present invention had IC_{50} values of less than 5µM in the hMCP-1 receptor binding assay described herein. For example compound 9 had an IC_{50} of 0.64µM.

[0154] No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

Example 10

Pharmaceutical Compositions

[0155] The following Example illustrates, but is not intended to limit, pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"). for therapeutic or prophylactic use in humans:

(a)

[0156]

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b)

[0157]

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c)

[0158]

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d)

[0159]

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium	1.5

(e)

[0160]

Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	to adjust pH to 7.6
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f)

[0161]

Injection II	(10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

(g)

[0162]

Injection III	(1mg/ml, buffered to pH6)
Compound X	0.1 % w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

(h)

[0163]

Aerosol I	mg/ml
Compound X	10.0

(continued)

Aerosol I	mg/ml
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

(i)

[0164]

Aerosol II	mg/ml
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j)

[0165]

Aerosol III	mg/ml
Compound X	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k)

[0166]

Aerosol IV	mg/ml
Compound X	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(l)

[0167]

Ointment	ml
Compound X	40 mg
Ethanol	300 µl

(continued)

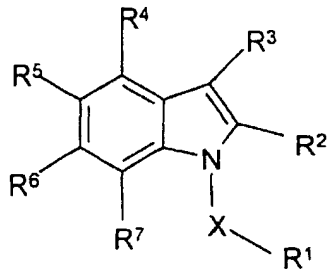
Ointment	ml
Water	300 µl
1-Dodecylazacycloheptan-2-one	50 µl
Propylene glycol	to 1 ml

Note:

[0168] Compound X in the above formulation may comprise a compound illustrated in Examples 1 to 6 herein. The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a) -(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

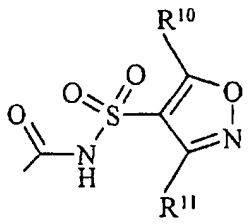
Claims

1. A compound of formula (I)



(I)

X is CH_2 or SO_2
R^1 is an optionally substituted aryl or heteroaryl ring;
R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tetrazol-5-yl, SO_3H, or a group of formula (VI)



(VI)

where R^8 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{12}$ where R^{12} is alkyl, aryl, heteroaryl, or haloalkyl, or R^8 is a group-$(CHR^{13})_r$-COOH where r is an integer of 1-3 and each R^{13} group is independently

selected from hydrogen or alkyl; R^9 is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl, aryl, heteroaryl or haloalkyl; R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl;

R^3 is hydrogen, a functional group, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkoxy, optionally substituted aralkyl, optionally substituted aralkyloxy, optionally substituted cycloalkyl;

R^4 is a group $C(O)NR^{15}R^{16}$ or a group $(CH_2)_tR^{17}$;

where R^{15} and R^{16} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl or optionally substituted heterocyclyl provided that R^{15} and R^{16} are not both hydrogen, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms;

R^{17} is selected from $NR^{18}R^{19}$, OR^{20} or $S(O)_sR^{21}$

where R^{18} and R^{19} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{18} and R^{19} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms;

R^{20} is substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl or optionally substituted heterocyclyl,

R^{21} is optionally substituted hydrocarbyl or optionally substituted heterocyclyl,

s is 0, 1 or 2 and t is an integer of from 1-4;

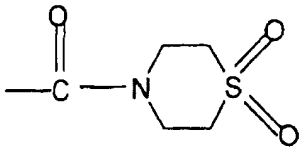
R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclyl groups,

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, or amide of the compound of formula (I).

2. A compound according to claim 1 where R^4 is a group $C(O)NR^{15}R^{16}$ where one of R^{15} or R^{16} is hydrogen or alkyl and the other is optionally substituted heterocyclyl or optionally substituted alkyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms.

3. A compound according to claim 2 wherein R^4 is a group $C(O)NR^{15}R^{16}$ where one of R^{15} or R^{16} is hydrogen and the other is heterocyclyl or alkyl substituted with one or more groups selected from amino, mono- or di-alkyl amino, carboxy or optionally substituted heterocyclyl.

4. A compound according to claim 2 wherein R^4 is a group $C(O)NR^{15}R^{16}$ and R^{15} and R^{16} together with the nitrogen atom to which they are attached form a morpholine ring, or R^4 is a group of sub-formula (IV)



5. A compound according to claim 1 wherein R^4 is preferably a group $(CH_2)_t$ R^{17} where t is 1 and R^{17} is a group $NR^{18}R^{19}$ and R^{18} and R^{19} are as defined in claim 1.

6. A compound according to any one of the preceding claims wherein R^1 is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

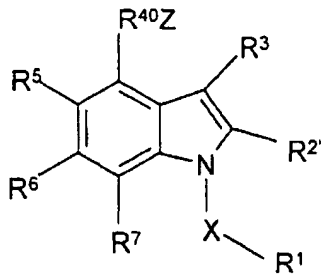
7. A compound according to any one of the preceding claims wherein X is CH_2.

8. A pharmaceutical composition comprising a compound according to any one of the preceding claims in combination with a pharmaceutically acceptable carrier.

9. A compound according to any one of claims 1 to 7 for use in the preparation of a medicament for use in the treatment of inflammatory disease.

10. A method of making a compound of formula (I) as defined in claim 1 which method comprises reacting a compound

of formula (VII)



(VII)

where X, R^1, R^3, R^3, R^6 and R^7 are as defined in relation to formula (I) and $R^{2'}$ is a group R^2 as defined in relation to formula (I) or a protected form thereof, R^{40} is a group C(O) or a group $(CH_2)_t$ where t is as defined in relation to formula (I) and Z is a leaving group,
either (a) when R^{40} is C(O), with a compound of formula (VIII)

$$HNR^{15}R^{16} \quad \text{(VIII)}$$

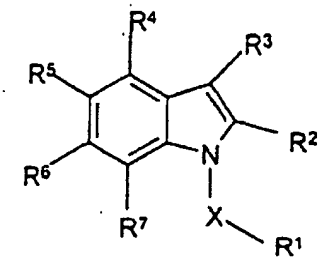
where R^{15} and R^{16} are as defined in relation to formula (I);
or (b) where R^{40} is group $(CH_2)_t$ with a compound of formula (IX)

$$HR^{17} \quad \text{(IX)}$$

where R^{17} is as defined in relation to formula (I);
and thereafter if necessary or desirable, deprotecting a group $R^{2'}$ to a group R^2 or changing a group R^2 to a different such group.

Patentansprüche

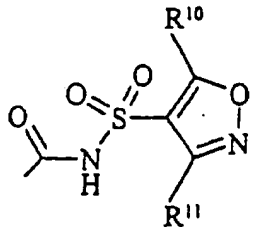
1. Verbindungen der Formel (I)



(I)

wobei
X für CH_2 oder SO_2 steht;
R^1 für einen gegebenenfalls substituierten Aryl- oder Heteroarylring steht;

R^2 für Carboxy, Cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, Tetrazol-5-yl, SO_3H oder eine Gruppe der Formel (VI)



(VI)

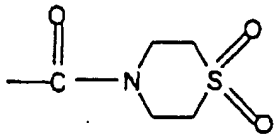
steht, wobei R^8 aus Wasserstoff, Alkyl, Aryl, Cyano, Hydroxy, $-SO_2R^{12}$, wobei R^{12} für Alkyl, Aryl, Heteroaryl oder Halogenalkyl steht, ausgewählt ist, oder R^8 für eine Gruppe $(CHR^{13})_r$-COOH steht, wobei r für eine ganze Zahl von 1-3 steht und die R^{13}-Gruppen jeweils unabhängig voneinander ausgewählt sind aus Wasserstoff und Alkyl;
R^9 für Wasserstoff, Alkyl, gegebenenfalls substituiertes Aryl, wie gegebenenfalls substituiertes Phenyl oder gegebenenfalls substituiertes Heteroaryl, wie 5- oder 6gliedrige Heteroarylgruppen, oder eine Gruppe COR^{14}, wobei R^{14} für Alkyl, Aryl, Heteroaryl oder Halogenalkyl steht, steht; R^{10} und R^{11} unabhängig voneinander aus Wasserstoff und Alkyl, insbesondere C_{1-4}-Alkyl, ausgewählt sind;
R^3 für Wasserstoff, eine funktionelle Gruppe, gegebenenfalls substituiertes Alkyl, gegebenenfalls substituiertes Alkenyl, gegebenenfalls substituiertes Alkinyl, gegebenenfalls substituiertes Aryl, gegebenenfalls substituiertes Heterocyclyl, gegebenenfalls substituiertes Alkoxy, gegebenenfalls substituiertes Aralkyl, gegebenenfalls substituiertes Aralkyloxy, gegebenenfalls substituiertes Cycloalkyl steht;
R^4 für eine Gruppe $C(O)NR^{15}R^{16}$ oder eine Gruppe $(CH_2)_tR^{17}$ steht;
wobei R^{15} und R^{16} unabhängig voneinander ausgewählt sind aus Wasserstoff, gegebenenfalls substituiertem Alkyl, gegebenenfalls substituiertem Alkenyl, gegebenenfalls substituiertem Alkinyl, gegebenenfalls substituiertem Cycloalkyl oder gegebenenfalls substituiertem Heterocyclyl, mit der Maßgabe, daß R^{15} und R^{16} nicht beide für Wasserstoff stehen, oder R^{15} und R^{16} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gegebenenfalls substituierten heterocyclischen Ring bilden, der gegebenenfalls weitere Heteroatome enthält;
R^{17} aus $NR^{18}R^{19}$, OR^{20} oder $S(O)_sR^{21}$ ausgewählt ist;
wobei R^{18} und R^{19} unabhängig voneinander ausgewählt sind aus Wasserstoff, gegebenenfalls substituiertem Hydrocarbyl und gegebenenfalls substituiertem Heterocyclyl, oder R^{18} und R^{19} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gegebenenfalls substituierten heterocyclischen Ring bilden, der gegebenenfalls weitere Heteroatome enthält;
R^{20} für substituiertes Alkyl, gegebenenfalls substituiertes Alkenyl, gegebenenfalls substituiertes Alkinyl, gegebenenfalls substituiertes Cycloalkyl oder gegebenenfalls substituiertes Heterocyclyl steht;
R^{21} für gegebenenfalls substituiertes Hydrocarbyl oder gegebenenfalls substituiertes Heterocyclyl steht;
s für 0, 1 oder 2 steht und t für eine ganze Zahl von 1-4 steht;
R^5, R^6 und R^7 unabhängig voneinander ausgewählt sind aus Wasserstoff, einer funktionellen Gruppe oder gegebenenfalls substituierten Hydrocarbylgruppen oder gegebenenfalls substituierten Heterocyclylgruppen,
und die pharmazeutisch unbedenklichen Salze, in vivo hydrolysierbaren Ester und Amide der Verbindungen der Formel (I).

2. Verbindungen nach Anspruch 1, wobei R^4 für eine Gruppe $C(O)NR^{15}R^{16}$ steht, wobei einer der Reste R^{15} und R^{16} für Wasserstoff oder Alkyl und der andere für gegebenenfalls substituiertes Heterocyclyl oder gegebenenfalls substituiertes Alkyl steht, oder R^{15} und R^{16} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gegebenenfalls substituierten heterocyclischen Ring bilden, der gegebenenfalls weitere Heteroatome enthält.

3. Verbindungen nach Anspruch 2, wobei R^4 für eine Gruppe $C(O)NR^{15}R^{16}$ steht, wobei einer der Reste R^{15} und R^{16} für Wasserstoff und der andere für Heterocyclyl oder Alkyl, substituiert durch eine oder mehrere Gruppen ausgewählt aus Amino, Mono- oder Dialkylamino, Carboxy und gegebenenfalls substituiertem Heterocyclyl, steht.

4. Verbindungen nach Anspruch 2, wobei R^4 für eine Gruppe $C(O)NR^{15}R^{16}$ steht und R^{15} und R^{16} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Morpholinring bilden, oder R^4 für eine Gruppe der Teilformel

(IV)



steht.

5. Verbindungen nach Anspruch 1, wobei R^4 vorzugsweise für eine Gruppe $(CH_2)_tR^{17}$ steht, wobei t für 1 steht und R^{17} für eine Gruppe $NR^{18}R^{19}$ steht und R^{18} und R^{19} wie in Anspruch 1 definiert sind.

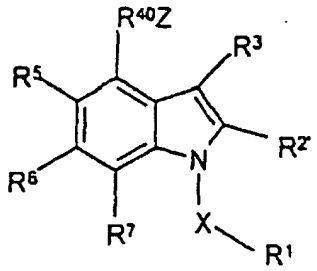
6. Verbindungen nach einem der vorhergehenden Ansprüche, wobei R^1 für 3,4-Dichlorphenyl, 3-Fluor-4-chlorphenyl, 3-Chlor-4-fluorphenyl oder 2,3-Dichlorpyrid-5-yl steht.

7. Verbindungen nach einem der vorhergehenden Ansprüche, wobei X für CH_2 steht.

8. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung nach einem der vorhergehenden Ansprüche zusammen mit einem pharmazeutisch unbedenklichen Träger.

9. Verbindungen nach einem der Ansprüche 1 bis 7 zur Verwendung bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von entzündlichen Erkrankungen.

10. Verfahren zur Herstellung einer wie in Anspruch 1 definierten Verbindung der Formel (I), bei dem man eine Verbindung der Formel (VII)



(VII)

in der X, R^1, R^3, R^5, R^6 und R^7 wie unter Formel (I) definiert sind und $R^{2'}$ für eine Gruppe R^2, wie unter Formel (I) definiert, oder eine geschützte Form davon steht, R^{40} für eine Gruppe C(O) oder eine Gruppe $(CH_2)_t$ steht, wobei t wie unter Formel (I) definiert ist, und Z für eine Abgangsgruppe steht,
entweder (a), wenn R^{40} für C(O) steht, mit einer Verbindung der Formel (VIII)

$$HNR^{15}R^{16} \quad \text{(VIII)}$$

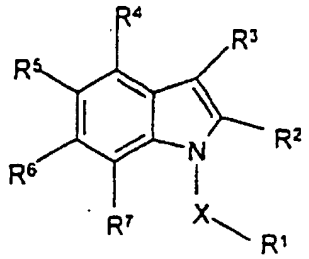
in der R^{15} und R^{16} wie unter Formel (I) definiert sind, umsetzt;
oder (b), wenn R^{40} für eine Gruppe $(CH_2)_t$ steht, mit einer Verbindung der Formel (IX)

$$HR^{17} \quad \text{(IX)}$$

in der R^{17} wie unter Formel (I) definiert ist, umsetzt; und anschließend, falls erforderlich oder gewünscht, eine Gruppe $R^{2'}$ zu einer Gruppe R^2 entschützt oder eine Gruppe R^2 in eine andere solche Gruppe umwandelt.

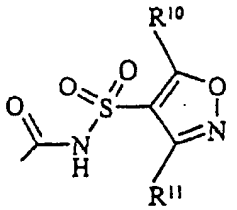
Revendications

1. Composé de formule (I)



(I)

X est CH_2 ou SO_2;
R^1 est un noyau aryle ou hétéroaryle éventuellement substitué;
R^2 est un groupe carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tétrazol-5-yle, SO_3H, ou un groupe de formule (VI)



(VI)

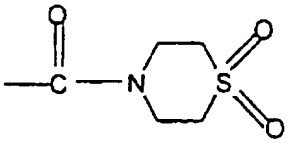
dans laquelle R^8 est choisi parmi un atome d'hydrogène et un groupe alkyle, aryle, cyano, hydroxy, $-SO_2R^{12}$, où R^{12} est un groupe alkyle, aryle, hétéroaryle ou halogénoalkyle, ou R^8 est un groupe $-(CHR^{13})_r-COOH$ dans lequel r est un nombre entier de 1-3 et chaque groupe R^{13} est choisi indépendamment parmi un atome d'hydrogène et un groupe alkyle; R^9 est un atome d'hydrogène ou un groupe alkyle, aryle éventuellement substitué tel que phényle éventuellement substitué ou hétéroaryle éventuellement substitué tel que les groupes hétéroaryle à 5 ou 6 chaînons, ou un groupe COR^{14}, dans lequel R^{14} est un groupe alkyle, aryle, hétéroaryle, ou halogénoalkyle; R^{10} et R^{11} sont choisis indépendamment parmi les atomes d'hydrogène et les groupes alkyle, en particulier alkyle en C_{1-4};
R^3 est un atome d'hydrogène, un groupe fonctionnel, un groupe alkyle éventuellement substitué, alcényle éventuellement substitué, alcynyle éventuellement substitué, aryle éventuellement substitué, hétérocyclyle éventuellement substitué, alcoxy éventuellement substitué, aralkyle éventuellement substitué, aralkyloxy éventuellement substitué, cycloalkyle éventuellement substitué;
R^4 est un groupe $C(O)NR^{15}R^{16}$ ou un groupe $(CH_2)_tR^{17}$;
où R^{15} et R^{16} sont choisis indépendamment parmi les atomes d'hydrogène et les groupes alkyle éventuellement substitué, alcényle éventuellement substitué, alcynyle éventuellement substitué, cycloalkyle éventuellement substitué ou hétérocyclyle éventuellement substitué, à condition que R^{15} et R^{16} ne soient pas tous deux des atomes d'hydrogène, ou bien R^{15} et R^{16}, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau hétérocyclique éventuellement substitué qui contient éventuellement d'autres hétéroatomes;
R^{17} est choisi parmi $NR^{18}R^{19}$, OR^{20} ou $S(O)_sR^{21}$;
où R^{18} et R^{19} sont choisis indépendamment parmi les atomes d'hydrogène et les groupes hydrocarbyle éventuel-

lement substitué ou hétérocyclyle éventuellement substitué, ou bien R^{18} et R^{19}, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau hétérocyclique éventuellement substitué qui contient éventuellement d'autres hétéroatomes;
R^{20} est un groupe alkyle substitué, alcényle éventuellement substitué, alcynyle éventuellement substitué, cycloalkyle éventuellement substitué ou hétérocyclyle éventuellement substitué,
R^{21} est un groupe hydrocarbyle éventuellement substitué ou hétérocyclyle éventuellement substitué,
s vaut 0, 1 ou 2 et t est un nombre entier de 1-4;
R^5, R^6 et R^7 sont choisis indépendamment parmi les atomes d'hydrogène et les groupes fonctionnels ou les groupes hydrocarbyle éventuellement substitué ou les groupes hétérocyclyle éventuellement substitué,
ou sel pharmaceutiquement acceptable, ester hydrolysable in vivo ou amide du composé de formule (I).

2. Composé selon la revendication 1, dans lequel R^4 est un groupe $C(O)NR^{15}R^{16}$ dans lequel un des radicaux R^{15} et R^{16} est un atome d'hydrogène ou un groupe alkyle et l'autre est un groupe hétérocyclyle éventuellement substitué ou alkyle éventuellement substitué, ou bien R^{15} et R^{16}, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau hétérocyclique éventuellement substitué qui contient éventuellement d'autres hétéroatomes.

3. Composé selon la revendication 2, dans lequel R^4 est un groupe $C(O)\ NR^{15}R^{16}$ dans lequel un des radicaux R^{15} et R^{16} est un atome d'hydrogène et l'autre est un groupe hétérocyclyle ou alkyle substitué par un ou plusieurs des groupes amino, mono- ou di-alkylamino, carboxy ou hétérocyclyle éventuellement substitué.

4. Composé selon la revendication 2, dans lequel R^4 est un groupe $C(O)NR^{15}R^{16}$ et R^{15} et R^{16}, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau morpholine, ou R^4 est un groupe de sous-formule (IV)



5. Composé selon la revendication 1, dans lequel R^4 est de préférence un groupe $(CH_2)_tR^{17}$, dans lequel t vaut 1 et R^{17} est un groupe $NR^{18}R^{19}$, et R^{18} et R^{19} sont tels que définis dans la revendication 1.

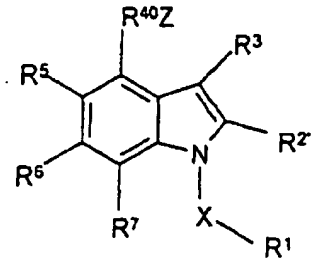
6. Composé selon l'une quelconque des revendications précédentes, dans lequel R^1 est un groupe 3,4-dichlorophényle, 3-fluoro-4-chlorophényle, 3-chloro-4-fluoro-phényle ou 2,3-dichloropyrid-5-yle.

7. Composé selon l'une quelconque des revendications précédentes, dans lequel X est CH_2.

8. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications précédentes en association avec un véhicule pharmaceutiquement acceptable.

9. Composé selon l'une quelconque des revendications 1 à 7 à utiliser dans la préparation d'un médicament à utiliser dans le traitement d'une maladie inflammatoire.

10. Procédé de fabrication d'un composé de formule (I) tel que défini dans la revendication 1, ce procédé comprenant le fait de faire réagir un composé de formule (VII)



(VII)

dans laquelle X, R^1, R^3, R^5, R^6 et R^7 sont tels que définis pour la formule (I) et $R^{2'}$ est un groupe R^2 tel que défini pour 1a formule (I), ou une forme protégée de celui-ci, R^{40} est un groupe C(O) ou un groupe $(CH_2)_t$,
dans lequel t est tel que défini pour la formule (I), et Z est un groupe partant,
soit (a) lorsque R^{40} est C(O), avec un composé de formule (VIII)

$$HNR^{15}R^{16} \qquad \text{(VIII)}$$

dans laquelle R^{15} et R^{16} sont tels que définis pour la formule (I);
soit (b) lorsque R^{40} est un groupe $(CH_2)_t$, avec un composé de formule (IX)

$$HR^{17} \qquad \text{(IX)}$$

dans laquelle R^{17} est tel que défini pour la formule (I);
et ensuite, si nécessaire ou si c'est souhaitable, déprotéger un groupe $R^{2'}$ en groupe R^2 ou remplacer un groupe R^2 en un tel groupe différent.